IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 10/569,583	First Named Inventor: Neil Gallagher
371 Filing Date: February 23, 2006	Attorney Docket No.: 101213-1P US
Examiner: Julie Ha	Group Art Unit : 1654
Customer No.: 44992	Confirmation No.: 5947
Title: Combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and an LHRH analogue and/or bisphosphonate	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.131

JON OWEN CURWEN declares:-

1. That he holds the degree(s) BSc (Hons) from Bradford University and MPhil awarded for work in association with the University of Bath and that he is an associate Principal Scientist in the Cancer and Infection Research Department of ASTRAZENECA UK Limited.

2. That he is an inventor on the above referenced patent application having the title of "Combination comprising N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide and an LHRH analogue and/or bisphosphonate" which has been assigned U.S. Patent Application Serial No. 10/569,583 and has an international filing date of September 10, 2004.

3. That he is the author of poster number 340 entitled "ZD4054: A Specific Endothelin A Receptor Antagonist With Potential Utility in Prostate Cancer and Metastatic Bone Disease" presented at AACR, Frankfurt, Germany between 19 and 22 November 2002 ("the Curwen Reference").

4. That he proposed studying the effects of combining the compound N-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide (ZD4054) with a bisphosphonate before November 2002 as evidenced by the e-mail to a potential collaborator in Amsterdam in Exhibit A.

5. That "study (c)" in Exhibit A states that he was interested in studying the effects of an ET_A receptor antagonist with a bisphosphonate.

6. That he met with the potential collaborator from Amsterdam to further discuss the proposed collaboration.

7. That a draft contract was prepared covering the proposed collaboration as evidenced by an e-mail (Exhibit B) from the Amsterdam group commenting on the draft contract.

8. That Exhibit B indicates that one of the proposed study for the collaboration was to study the effects of bisphosphonates on ET-1/ZD4054 response (Exhibit B, Plan of Investigation, (C) exploratory studies).

9. That whilst negotiations with the Amsterdam collaborators were taking place he identified a preclinical mouse model held by Williams et al. in Australia, which was potentially useful in the study of ZD4054.

10. That he entered into discussions with the Williams et al group as evidenced in Exhibit C, where he expressed a desire to study the effects of combining ZD4054 with a bisphosphonate.

11. That in the e-mail in Exhibit C he stated:

> *"I can justify a study in a model with proven sensitivity to bisphosph's with 2 monotherapy arms (4054, bisphosph) and a combination arm. Interesting data from this would then justify later studies (bigger?)."*

12. That negotiation of a contract to carry out the proposed studies took place with the Williams as evidenced by the correspondence in Exhibit D.

13. That the studies were carried out by the Williams group which led to the publication of the Williams et al paper (Eur J. Cancer Suppl. 2006; 4(12):15) of the results in this model of combining ZD4054 with the bisphosphonate pamidronate.

14. That priority application number GB 0320806.3 was filed at the UK Patent Office on September 5, 2003 disclosing a combination comprising ZD4054 and a bisphosphonate.

15. These facts demonstrate that the invention of a combination, comprising ZD4054 and a bisphosphonate was conceived before the Curwen Reference was presented in November 2002 and that the inventors diligently pursued the invention from the date of conception of the invention at least until filing of the priority application of U.S. Patent Application Serial No. 10/569,583 and the reduction to practice of the invention.

16. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and on belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both, under section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of U.S. Application Serial No. 10/569,583.

Jon Owen Curwen

Dated: 15th August 2008

Address: AstraZeneca
Mereside
Alderley Park
Macclesfiled
SK10 4TG
United Kingdom

Exhibit A

(A)

Curwen, Jon O

From: Curwen, Jon O
Sent: [redacted]
To: 'ER.Burger.OCB.ACTA@med.vu.nl'
Subject: AstraZeneca interest in bone studies.

Dr Burger,

I am a colleague of Dr Clive Morris of AstraZeneca. If you remember, Clive contacted you last year expressing his interest in your studies of cultured human osteoblasts. You said "We are in principle interested in collaborations with industry, but I need of course a lot more information before anything definitive can be decided".

I would like to follow this up with you if I may. To give you some detail, I would be interested in the following types of study:

(a) a study of the effect of human endothelin-1 (ET-1) on human osteoblastic cultures and the reversal of these effects by a selective ETa receptor antagonist.

(b) a study of the effects of the ETa receptor antagonist on non-ET-1 stimulated osteoblastic growth (either basal growth or stimulated by another natural growth factor).

(c) the studies described above in the presence of a bisphosphonate compound.

Would you be interested in collaborating on these studies with us ? If you would like more detail please get in touch.

I look forward to your reply.

Regards,
Jon

Jon Curwen
Associate Team Leader
Cancer Bioscience

Cancer and Infection Research Area,
AstraZeneca Pharmaceuticals,
Mereside,
Alderley Park,
Macclesfield,
Cheshire, U.K.

Tel +44 (0)1625 230752
Fax +44 (0)1625 513624
E-mail Jon.Curwen@astrazeneca.com

Exhibit B

B

Nelson, Mike A (Alderley Park UK)

From: J.Klein_nulend.OCB.ACTA@med.vu.nl
Sent: [redacted]15:23
To: Curwen, Jon O
Cc: M.Mullender.Ocb.ACTA@med.vu.nl; ALJJ.Bronckers.OCB.ACTA@med.vu.nl
Subject: re: draft proposal Amsterdam-AstraZeneca study

Follow Up Flag: Follow up
Flag Status: Flagged

Amsterdam
greement (draft).do.

Dear Jon,

Hereby I am sending you as an attached file the draft proposal of the Amsterdam-AstraZeneca study for your consideration. We have added some details and filled up spaces that you had left. In addition, we have taken the freedom to propose a 2 year study and added a financial paragraph for these 2 years. I am looking forward to your comments.

Sincerely,
Jenneke Klein-Nulend

Jenneke Klein-Nulend, PhD
ACTA-Vrije Universiteit, Dept Oral Cell Biology
Van der Boechorststraat 7, NL-1081 BT Amsterdam
The Netherlands
tel: 31-20-4448660 - fax: 31-20-4448683
e-mail: J.Klein_Nulend.ocb.acta@med.vu.nl

Exhibit C

RE St V's Melbourne - Draft proposal

From: Moore, George
Sent: [redacted]
To: Green, Tim P; Curwen, Jon O; Wilbraham, Jackie M
Cc: Walker, Linda A
Subject: RE: St V's Melbourne - Draft proposal

Thanks Tim

Jackie, could you keep me informed about any agreements reached with this group, and any others agreements that we may be contemplating with groups in Australia.

The recently announced Federal Budget may be opening opportunities for local tax deductions as incentives for new R&D investment by the Pharma Industry in Australia. Government has not informed the details as yet.

Regards

George

-----Original Message-----
From: Green, Tim P
Sent: Friday, [redacted] 10:45 PM
To: Moore, George; Curwen, Jon O; Wilbraham, Jackie M
Cc: Walker, Linda A
Subject: RE: St V's Melbourne - Draft proposal

stalled slightly - mostly my fault (but AACR cancellation didn't help)

back on track now. Elizabeth is sending me some lysates from her cells so that we can test for Src and phosphosubstrates of Src - if we get a positive result we will go ahead with testing in her in vivo model (I have had this OK'd by my Collaborations team)

I am also sending Rik Thompson a sample of another Src inhibitor to test in some in vitro models of his (no cost to us, it is more of tool to help them understand some pathway components in their breast tumour cells)

Jon is also keen to press ahead with his compound studies

Cheers

Tim

-----Original Message-----
From: Moore, George
Sent: [redacted]
To: Green, Tim P; Curwen, Jon O; Wilbraham, Jackie M
Subject: St V's Melbourne - Draft proposal

Hi Folks

What is the status??

George

-----Original Message-----
From: edw@medstv.unimelb.edu.au [mailto:edw@medstv.unimelb.edu.au]
Sent: Thursday, 27 March 2003 12:00 PM
To: Green, Tim P
Cc: rik@medstv.unimelb.edu.au; Moore, George; Adams, Julie L (Cancer & Infection); Curwen, Jon O; Wilbraham, Jackie M; Gaughan, Emily R; Fennell, Michael
Subject: RE: Draft proposal

Hi all

I have attached our responses to the questions raised by Tim and Jon as a word document (with the red text as our responses). The planning phase is very important to maximise the potential of any future collaboration. We are delighted to play a role during this phase, and are also fundamentally interested in the baseline data you are seeking.
Look forward to seeing you (Tim & Jon) at AACR.
Kind regards
Elizabeth

> Dear Elizabeth and Rik,
>
> First of all please let me apologise for the delay in replying to your
> prompt response and draft outlining options for testing our development
> compounds in your model of Osteosclerotic bone metastasis.
>
> As Jon and I explained during our tele conference - for different reasons
> we
> are keen obtain timely data on our respective compounds in a model of
> Osteosclerotic bone metastasis. The model you have developed certainly
> looks
> attractive in this respect, although we both have a few questions that
> would
> need addressing if we are to progress to the types of in vivo studies you
> suggest.
>
>
> First of all my questions (Tim):
>
> I am a little unsure as to the origin of the B103 cell line - is it
> prostate
> in origin - or bladder?
>
> I would like to see some evidence that Src kinase is present (and active)
> in
> your B103 cells. I think this would be particularly important if we were to
> carry out studies in the preventative type setting you suggest.
>
> 1.Could you run a Western and blot for active Src/Src phospho substrates -
> we could provide you with lysate conditions and supply or advise
> on appropriate antibodies to use.
>
> 2.Have you any B103 based in vitro assays (I'm particularly thinking about
> migration, invasion and proliferation assays)
> that we could test our Src inhibitor in? - again to build the case for
> testing in vivo in a preventative setting
>
> If you are not able to do these in vitro studies - then is there an option
> to send us either cells - or cell lysates for us to check out Src
> activity?.
>
> If it emerges Src is not present and active in these cells (or it is not
> possible to carry out these preliminary experiments) - then we would most
> likely still want to test our Src inhibitor in the treatment type setting
> you suggest (because here our predominant target would be Src activity in
> osteoclasts during the lytic phase of metastases).
>
> I hope these questions make sense.....
>
>
> Here are Jon Curwen's comments and questions:
>
> At the moment (in the B103 model specifically) I have little feel for the
> involvement of Endothelin (ET) in the osteoblastic effects they are seeing.
> Due to this I can't justify ploughing straight into two big intervention
> and
> prevention studies without supportive data.
>
> There are a couple of approaches we can take to get this supportive data

> :
>
> (1) in vitro assessment of the ET-1 production of the cells - we could look
> at their cells in our assays if there was no IP in the way (or is this
> something that could be carried out in Melbourne -)
>
> or....
>
> (2) we need to look at a bisphosphonate combination to show that 4054
> doesn't mess up the efficacy of the bisphosph anyway regardless of any ET-1
> involvement. Even as things stand now I can justify a study in a model with
> proven sensitivity to bisphosph's with 2 monotherapy arms (4054, bisphosph)
> and a combination arm. Interesting data from this would then justify later
> studies (bigger?).
>
> So - all in all I need more of a structured plan before launching into
> the
> big tests as currently proposed with the consideration above taken into
> account.
>
>
> The above is brief but an essential first consideration from my
> perspective.
>
>
>
> We look forward to your response
>
> Tim Green & Jon Curwen
>
>
> P.S where are you staying in Toronto next week? - would you still like to
> meet up with us (maybe go out for a bite to eat?)
>
>
> -----Original Message-----
> From: edw@medstv.unimelb.edu.au [mailto:edw@medstv.unimelb.edu.au]
> Sent: [redacted]
> To: Wilbraham, Jackie M
> Cc: Moore, George; Green, Tim P; rik@medstv.unimelb.edu.au; Adams, Julie
> L (Cancer & Infection); Curwen, Jon O
> Subject: Draft proposal
>
>
> Hi all
>
> Attached is a our draft proposal document for the testing of AstraZeneca
> compounds in our bone metastasis models. As discussed on friday, this
> document
> is a starting point for discussion so please feel free to provide input/ask
>
> questions/suggest refinements.
>
> Regards
> Elizabeth
>
> ---
> This mail sent through IMP: http://horde.org/imp/
>

This mail sent through IMP: http://horde.org/imp/

Exhibit D

(D)
CONF EMAIL

From: Curwen, Jon O
Sent: [redacted]
To: Brooks, Nigel AN
Subject: Melbourne group (bisphosphonate) background

Nigel,

here's the draft proposal with some description of rationale, this was discussed face-to-face with Elizabeth at the src/4054 bone Ad-board in December 03:

Curwen proposal Dec 2003.doc

A draft Institution agreement was sent back in November 03 - comments on this have just been sent back to Rachael Pteeth (11th May 04).

Key updates to the scientific proposal are contained in more recent e-mails:

[redacted]

Hi Elizabeth,

thanks for the updated proposal. Apologies for the long delay in replying - but I've been very busy at home with our new baby son Ben (aged 4 weeks exactly today). Either that or trying to catch up on sleep!

On the proposal and your specific questions:

I'm happy just to bank plasma samples as I think the compound levels will be the key measure to interpret the histomorphometry data. Hopefully this is more realistic from a practical point of view given the sampling limitations from a mouse.

I'd like to keep the second study in the proposal with the wording you sent ("with refinement of the second round to confirm and extend promising observations"). For ease of costing, I'd be tempted to consider the second study as having the same total resource requirements as the first version but with some flexibility on how the group numbers and sizes are distributed within that total.

I'm in the process of finalising what bisphosphonate we should use (there is some issue with pinning clinicians down to a final choice!) .Hopefully I can clarify soon and then confirm doses etc as you've requested.

A couple of questions from me. Firstly, how is the legal agreement coming along? Anything we can do to help from this side? Secondly - on the efficiency of the intra-cardiac inoculation technique. Can you please let me know what success rate you have with the inoculation of cells via this route and if there are any particular welfare issues you have to check for (and when do you intervene)? I'd like to have this info as its a technique we don't carry out and I'd like to have some

answers if questioned on it by ethics panels etc.

Thanks,
Jon

[redacted]

Elizabeth,

apologies for the delay (again), hope you are well. I'm adapting to baby-induced insomnia but he's "slept through" a couple of times recently so maybe a more normal sleep pattern could be possible soon.

Anyway, the good news is that I can finally state we'd like to use pamidronate as the bisphosphonate in our proposed studies. I haven't yet tracked down a suitable dose to use in the preclinical work yet but I thought the best place to start would be to ask if you have insight from work with your model?

I've recently been pushed by our collaborations group saying that they need a scientific proposal asap. I assume this means that the agreement between institutions is looking OK. Is this your perception too?

Looking forward to hearing from you,

Jon.

I haven't had a reply to this last message yet - but I'll send a new message to follow up to try to get things moving and also do the introduction of you as new contact.

Cheers,
Jon

Jon Curwen
Team Leader
Cancer Bioscience
12F20 Mereside
30752

RE AZ endothelin studies

From: Curwen, Jon O
Sent: [redacted]
To: 'edw@medstv.unimelb.edu.au'
Subject: RE: AZ endothelin studies

Hi Elizabeth,

thanks for the updated proposal. Apologies for the long delay in replying - but I've been very busy at home with our new baby son Ben (aged 4 weeks exactly today). Either that or trying to catch up on sleep!

On the proposal and your specific questions:

I'm happy just to bank plasma samples as I think the compound levels will be the key measure to interpret the histomorphometry data. Hopefully this is more realistic from a practical point of view given the sampling limitations from a mouse.

I'd like to keep the second study in the proposal with the wording you sent ("with refinement of the second round to confirm and extend promising observations"). For ease of costing, I'd be tempted to consider the second study as having the same total resource requirements as the first version but with some flexibility on how the group numbers and sizes are distributed within that total.

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A couple of questions from me. Firstly, how is the legal agreement coming along? Anything we can do to help from this side? Secondly - on the efficiency of the intra-cardiac inoculation technique. Can you please let me know what success rate you have with the inoculation of cells via this route and if there are any particular welfare issues you have to check for (and when do you intervene)? I'd like to have this info as its a technique we don't carry out and I'd like to have some answers if questioned on it by ethics panels etc.

Thanks,
Jon

-----Original Message-----
From: edw@medstv.unimelb.edu.au [mailto:edw@medstv.unimelb.edu.au]
Sent: [redacted]
To: Curwen, Jon O
Subject: Re: AZ endothelin studies

Hi Jon

Happy new year to you too! Hope you are well. I have just returned for summer holidays in Tasmania - no mobile phone, internet...so work is a bit of a shock!

the proposal is looking good.
Could you please confirm if you need serum or plasma banked (e.g. for measuring circulating drug concentrations or a biomarker, in the bone met study serum for markers of bone turnover). It is hard to get enough blood from each mouse to do both!

I agree that fewer mice could be used in the first study. I have suggested 6 mice / arm. (I our experience this is usually enough for statistical analysis of histomorphometrical endpoints)

Could you let me know if you want the second study repeated so I can calculate the budget. (I don't think we would need to do the first study twice, but there is the added variabilty of the tumour cells in the second expt).

How many doses (and mice per dose) do you think we would need in the

preliminary bisphosphonate dose finding expt? (And any luck finding a source of bisphosphonate to purchase at your end?)

BTW, as to the contract, I have given the laywer process another nudge at this end, so it's still moving!

best regards
Elizabeth

Quoting "Curwen, Jon O" <Jon.Curwen@astrazeneca.com>:

> Elizabeth,
>
> (belated) happy new year. Hope you had a great Christmas.
>
> Before the Christmas break I sent you a "pre-draft" version of a protocol
> for the endothelin studies based on what we discussed in Texas ready for you
> to sanity check. I've attached it below. I've since realised that a number
> of things I sent pre-Xmas haven't made it out through the AZ firewall, so in
> case the e-mail to you was one of those affected, I thought I should send
> this again.
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> Apologies if this follow up isn't required - I've found that not all the
> bounced e-mails have been flagged back, so I'm possibly being overcautious.
>
> <<LW proposal[redacted].doc>>
> Kind Regards,
> Jon
>
>
> Jon Curwen
> Translational Science Leader
> Cancer Bioscience
>
> Cancer and Infection Research Area,
> AstraZeneca Pharmaceuticals,
> Mereside,
> Alderley Park,
> Macclesfield,
> Cheshire, U.K.
>
> Tel +44 (0)1625 230752
> Fax +44 (0)1625 513624
> E-mail Jon.Curwen@astrazeneca.com
>
>

From: Curwen, Jon O
Sent: [redacted] 17:39
To: 'edw@medstv.unimelb.edu.au'
Subject: RE: AZ endothelin studies

Elizabeth,

apologies for the delay (again), hope you are well. I'm adapting to baby-induced insomnia but he's "slept through" a couple of times recently so maybe a more normal sleep pattern could be possible soon.

Anyway, the good news is that I can finally state we'd like to use pamidronate as the bisphosphonate in our proposed studies. I haven't yet tracked down a suitable dose to use in the preclinical work yet but I thought the best place to start would be to ask if you have insight from work with your model?

I've recently been pushed by our collaborations group saying that they need a scientific proposal asap. I assume this means that the agreement between institutions is looking OK. Is this your perception too?

Looking forward to hearing from you,

Jon.

-----Original Message-----
From: edw@medstv.unimelb.edu.au [mailto:edw@medstv.unimelb.edu.au]
Sent: [redacted] 07:19
To: Curwen, Jon O
Subject: RE: AZ endothelin studies

Hi Jon

Congratulations!

All your comments sound fine.

I will have to put in an ethics application here to do these experiments, but I have pasted in some text from a previous application below. With these cells we expect that 50% of inoculated mice will develop bone mets (it is 100% with our next generation cell line, but that is very metastatic and the mice develop a large soft tissue tumour burdern that means we have to harvest them). If you need any more detail let me know.

Elizabeth

General Anaesthetic
Ketamine (40 ug/g/mouse)/Xylazine (16 ug/g mouse) i.p. followed by isoflurane inhalation (delivered using a paediatric anaesthetic machine and a nose cone) as required. The depth of anaesthesia will be monitored by the absence of reflex in the toe pinch test. Vapour is trapped by a carbon trapping device attached to the anaesthetic machine.

Intracardiac inoculation:
Cells are loaded into a 1ml syringe, and a 26 gauge needle fitted. The needle is inserted into the left ventricle by puncturing the skin blow the sternum and moving the needle into the thoracic cavity. Once the needle enters the ventricle, pulsating, bright red blood is observed, and 0.1ml cell solution is slowly injected into the heart.

Recovery from general anaesthetic:
Mice are wrapped in a clean tissue (to maximize heat conservation) and moved to a clean cage, which is in turn placed on a heated pad. Mice are inspected every 15 minutes until fully ambulant and alert, at which time they are

returned to their regular cage.

General monitoring of mouse well being:
Mice will be inspected daily for any signs of distress or changes in mobility. Mice will also be weighed twice weekly to monitor weight gain (as an indicator of general health).

Harvesting of mice
Mice will be harvested 3 weeks after the first observation of osteoblastic bone metastasis. This is likely to be 7 weeks after the inoculation of tumour cells. Should any animal show any signs of distress (e.g. weight loss, ruffled fur) they will be harvested immediately. On the day of harvest, mice will be anaesthetized as described above (General Anaesthetic), a final X-ray film taken and blood collected by cardiac puncture, and subsequently killed by anaesthetic overdose (repeat Ketamine/Xylazine i.p. injection as described in General Anaesthetic. When this dose is administered to the mice which have had a blood volume approximately 5% of body weight collected by cardiac puncture they succumb to anaesthetic overdose). Mouse bones and other tissues will then be dissected, prepared for histological analysis and DNA extraction to assess tumour burden

Quoting "Curwen, Jon O" <Jon.Curwen@astrazeneca.com>:

> Hi Elizabeth,
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> thanks for the updated proposal. Apologies for the long delay in replying
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> Sent: [redacted]
> To: Curwen, Jon O
> Subject: Re: AZ endothelin studies
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> end, so it's still moving!
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> Elizabeth
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> > Elizabeth,
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> > Jon
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> >
> > Jon Curwen
> > Translational Science Leader
> > Cancer Bioscience
> >
> > Cancer and Infection Research Area,
> > AstraZeneca Pharmaceuticals,
> > Mereside,
> > Alderley Park,
> > Macclesfield,
> > Cheshire, U.K.
> >
> > Tel +44 (0)1625 230752
> > Fax +44 (0)1625 513624
> > E-mail Jon.Curwen@astrazeneca.com
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